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New samarium diiodide-induced cyclizations*

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Abstract: Samarium diiodide (SmI_2) smoothly promotes the cyclizations of suitably substituted carbonyl compounds with styrene subunits leading to benzannulated cyclooctenes. The intramolecular samarium ketyl addition to arene or hetarene moieties enables a new, efficient, and highly stereoselective entry to dearomatized products such as hexahydronaphthalenes, steroid-like tetra- or pentacyclic compounds, or dihydroindole derivatives. The usefulness of the developed SmI_2-induced cyclization method was demonstrated by the shortest formal total synthesis of the alkaloid strychnine.

Keywords: alkenes; alkynes; arenes; cyclooctene derivatives; dearomatization; hetarenes; hexahydronaphthalenes; indoles; ketyls; natural products; samarium diiodide; steroid-like compounds; strychnine.

INTRODUCTION

Owing to the pioneering studies of Kagan et al. [1], easily generated samarium diiodide (SmI_2) is nowadays employed as reagent in many applications in organic chemistry [2]. One of its key features is the generation of samarium ketyls from carbonyl compounds, which can undergo subsequent coupling reactions with other π-systems. Pinacol-type reactions are well known, however, samarium ketyl-alkene and -alkyne couplings certainly have higher importance. The intramolecular versions of these additions often lead to highly substituted cyclic products in a stereoselective fashion, and hence these processes have been applied to a variety of syntheses, including complex natural products [3]. Mechanistically, SmI_2 transfers one electron to the carbonyl group to generate the required samarium ketyl. Very often, the strong Lewis base hexamethylphosphoramide (HMPA) is required to shift the equilibria to the side of the samarium ketyl and subsequently to the products. A second equivalent of SmI_2 generally transforms the intermediate product radicals into anions which are trapped by a proton source or other electrophiles. In this review, we want to report on our own endeavors to generate interestingly functionalized carbo- and heterocyclic compounds by use of SmI_2. Figure 1 summarizes typical products and the corresponding precursors of the crucial coupling step [4].

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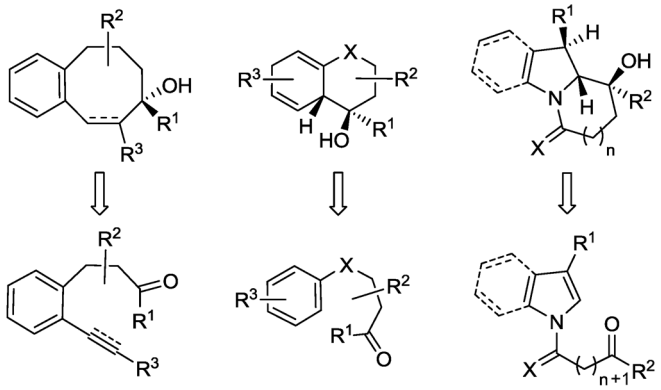
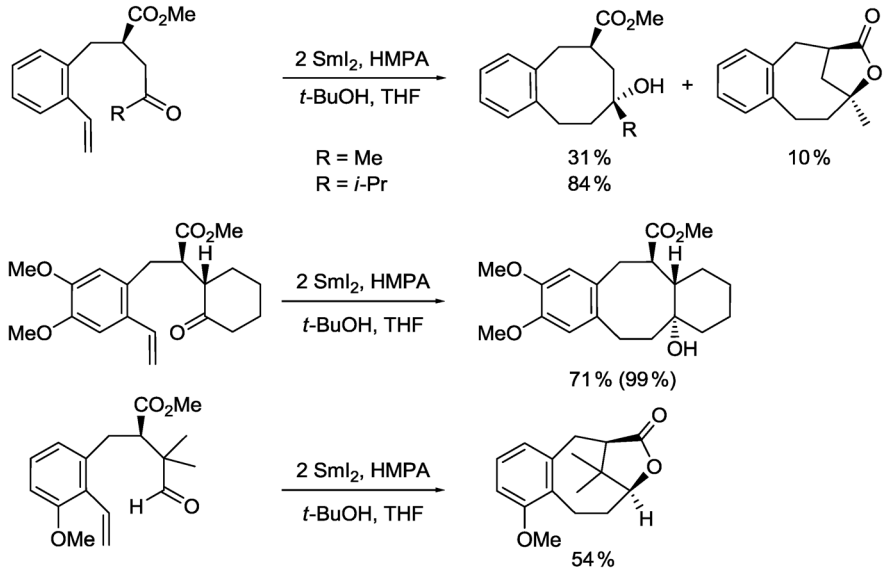


Fig. 1 Retrosynthetic analysis of cyclooctene, hexahydronaphthalene, hexahydroquinoline, or dihydroindole derivatives via SmI_2-induced ketyl-(het)arene couplings.

RESULTS AND DISCUSSION

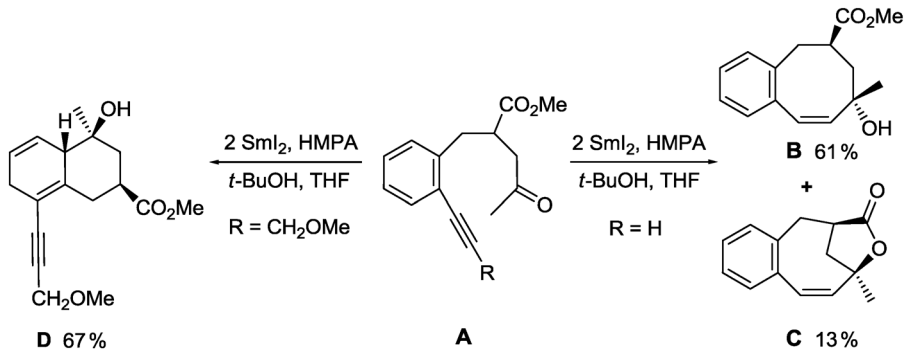
Synthesis of carbocycles

As mentioned in the introduction, the cyclizations of samarium ketyls to alkene moieties are well-known processes and are employed in many applications. Some time ago we were interested in the generation of benzannulated 8-membered rings and planned to employ SmI_2 for this purpose. Gratifyingly, the anticipated 8-*endo-trig* cyclizations of styrene derivatives smoothly led to a variety of benzannulated cyclooctene derivatives (Scheme 1) [5]. The stereoselectivities of these transformations are moderate to excellent. More recently, we also investigated the formation of rings larger than 8-membered and found surprisingly high efficacy and stereoselectivity in many examples [6].



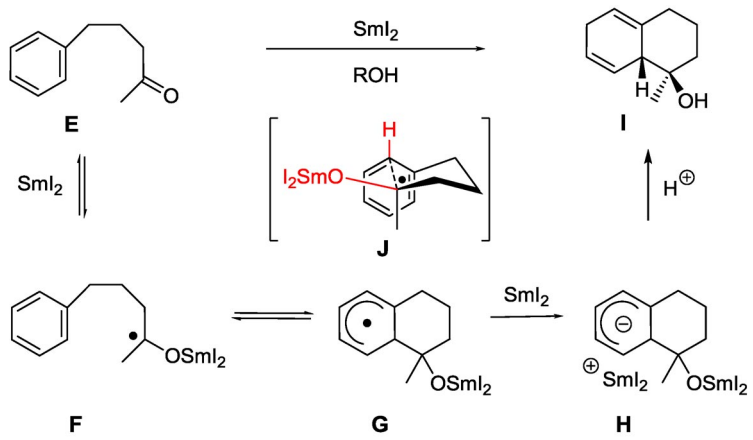
Scheme 1 Reductive cyclization of alkenes to benzannulated cyclooctene derivatives.

We subsequently extended these SmI_2-induced couplings to alkynes as ketyl accepting units. This endeavor was successful in many cases, one example of an 8-*endo-dig* reaction being illustrated in Scheme 2 [7]. However, only ketones **A** with a monosubstituted alkyne unit furnished the expected benzannulated cyclooctane derivatives **B** and **C**, whereas terminally substituted alkynes underwent a new reaction mode. Now hexahydronaphthaline derivatives of type **D** were isolated with excellent diastereoselectivity (Scheme 2) [8]. Although there are a few related transformations known in the literature, these ketyl-arene couplings are novel and include a synthetically valuable reductive dearomatization step [9].



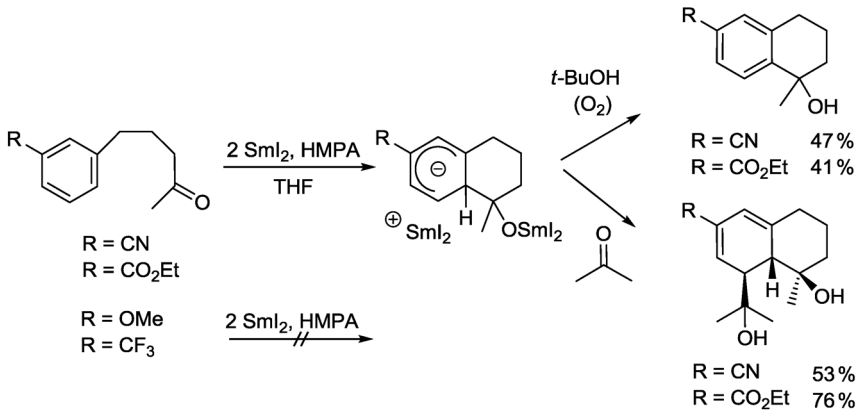
Scheme 2 Reductive SmI_2-induced ketyl-alkyne coupling vs. ketyl-arene coupling.

The proposed mechanism for the ketyl-arene coupling is depicted in Scheme 3. After (reversible) formation of the samarium ketyl **F** the intramolecular addition to the arene moiety furnishes a cyclohexadienyl radical of type **G**. A second electron transfer from SmI_2 generates the corresponding anion **H**, which is regioselectively protonated analogously to the Birch reduction to yield the kinetically controlled unconjugated 1,4-cyclohexadiene substructure. The configuration of the product can plausibly be explained by the chair-like transition state **J** (Scheme 3) with the bulky samariumoxy substituent in the more favorable equatorial position.



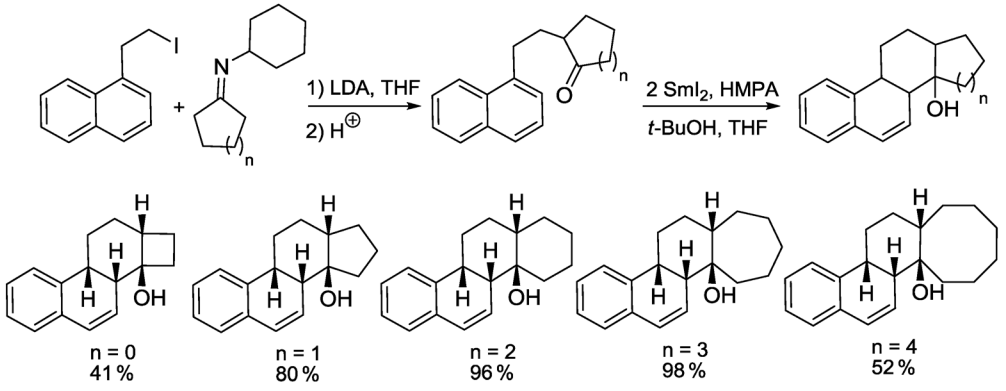
Scheme 3 Proposed mechanism of the SmI_2-induced reductive ketyl-arene coupling.

After the serendipitous finding of this novel dearomatizing reaction, we systematically studied the influence of substituents at both sides of the γ-aryl ketones. We also modified the distance between the carbonyl group and the ketyl accepting arene ring [10]. Substituents in *meta* position of the arene are particularly characteristic (Scheme 4). Whereas a methoxy or a trifluoromethyl substituent strongly hampers the reaction, electron-withdrawing groups such as cyano or ethoxycarbonyl facilitate the samarium ketyl-arene cyclization (Scheme 4). After standard work-up conditions, the reoxidized products were isolated, however, when the experiments were performed without proton source the intermediate cyclohexadienyl anion could be trapped by electrophiles such as acetone, providing nicely functionalized products in a simple fashion [10]. Parallel to our studies, Tanaka et al. investigated similar cyclizations of β-, γ-, and δ-aryl ketones being disubstituted at the arene moiety [11]. Their examples impressively demonstrate the potential of the ketyl-arene cyclization for the construction of highly substituted synthetically valuable carbocyclic compounds.



Scheme 4 Examples of typical SmI_2-induced ketyl-arene couplings.

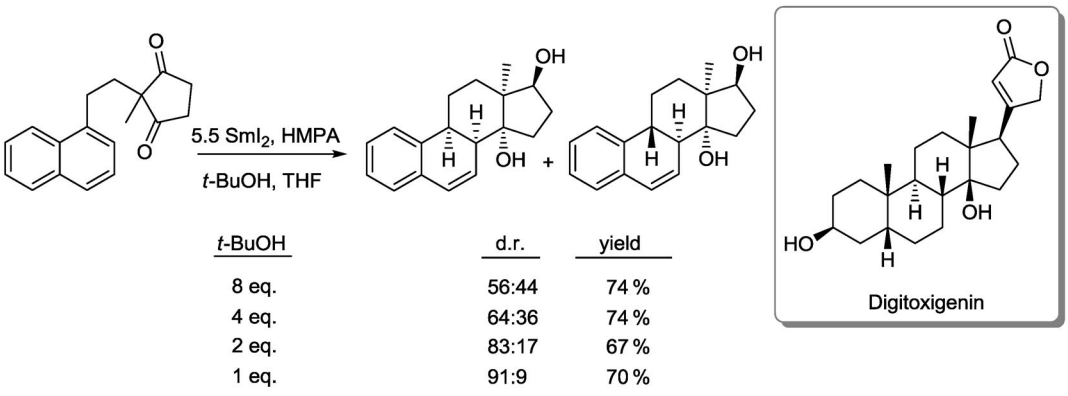
The extension of our method to naphthalene derivatives was an obvious step during the exploration of scope and limitation of this addition to aromatic units. Fortunately, the precursors for these experiments were easily available by azaenolate alkylation followed by hydrolysis, and the ketyl-naphthene cyclization proceeded very smoothly in most cases (Scheme 5) [12]. The desired tetracyclic compounds were formed in diastereomerically pure form with rings B/C and C/D being fused in *cis-cis*



Scheme 5 Synthesis of steroid-like tetracycles.

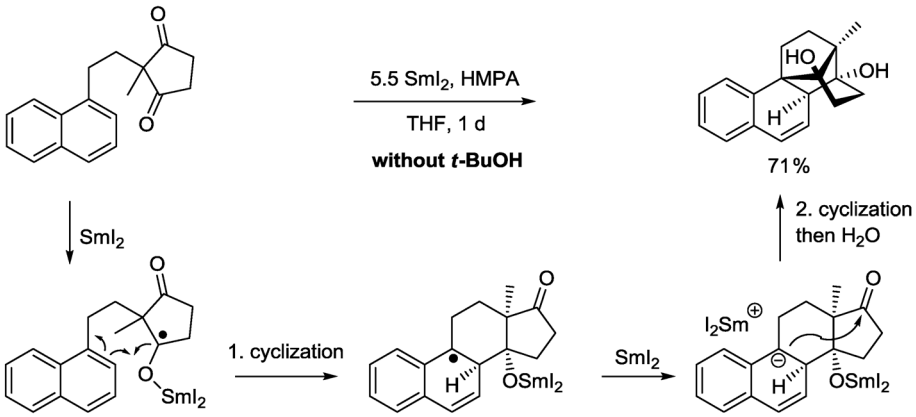
fashion. This leads to a bowl shape of the resulting steroid-like tetracyclic products. It should be emphasized that the styrene subunit of the products allows flexible subsequent synthetic elaborations, hence allowing a versatile access to highly substituted steroid analogues.

The use of cyclopenta-1,3-dione derivatives as samarium ketyl precursors allowed the preparation of tetracyclic compounds closely resembling steroids in ring D (Scheme 6) [13]. Since two carbonyl groups are involved in this process, at least 4 equiv of SmI_2 are required to obtain good yields. Surprisingly, the stereoselectivity of the process was strongly dependent on the amount of *t*-butanol employed as proton source, with the best result being obtained with just 1 equiv of the alcohol [13]. The obvious experiment without any proton source unexpectedly generated a fascinating pentacyclic compound in good yield. A plausible mechanism for the formation of this cyclization product is proposed in Scheme 7 [14]. Again, the styrene-type substructure in this product allowed the generation of a small library of highly substituted rigid steroid-related compounds (Scheme 8).

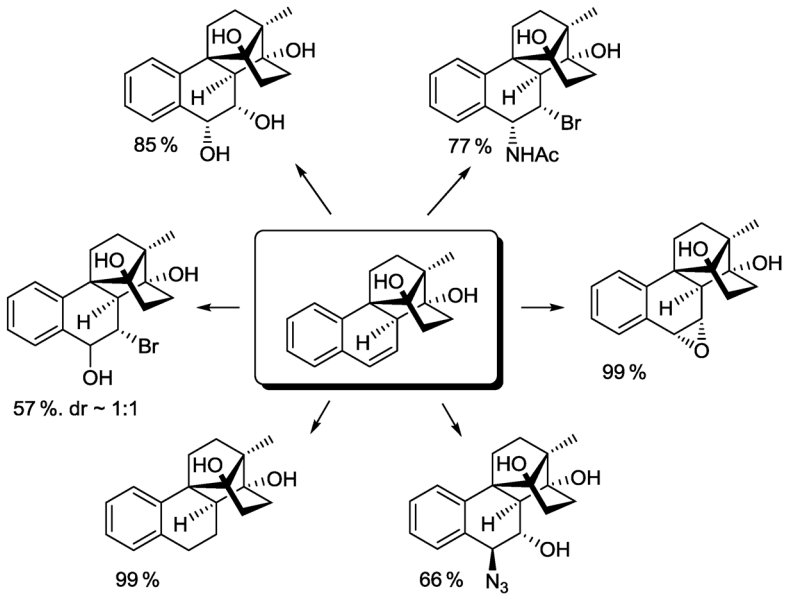


t-BuOH	d.r.	yield
8 eq.	56:44	74 %
4 eq.	64:36	74 %
2 eq.	83:17	67 %
1 eq.	91:9	70 %

Scheme 6 SmI_2-induced cyclization of a naphthyl-substituted cyclopenta-1,3-dione.



Scheme 7 Cyclization of the naphthyl-substituted cyclopenta-1,3-dione without proton source.

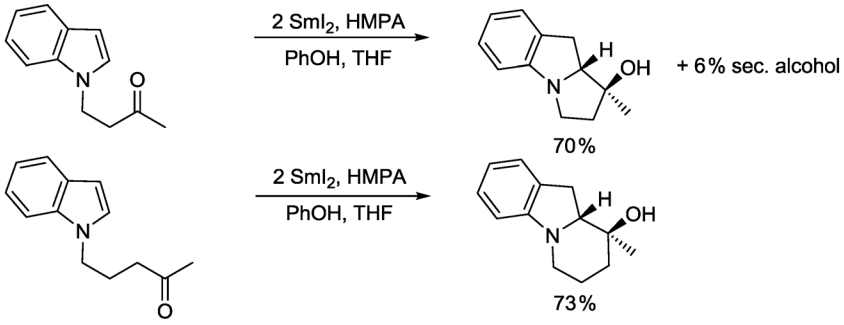


Scheme 8 Addition reactions to the pentacyclic compound.

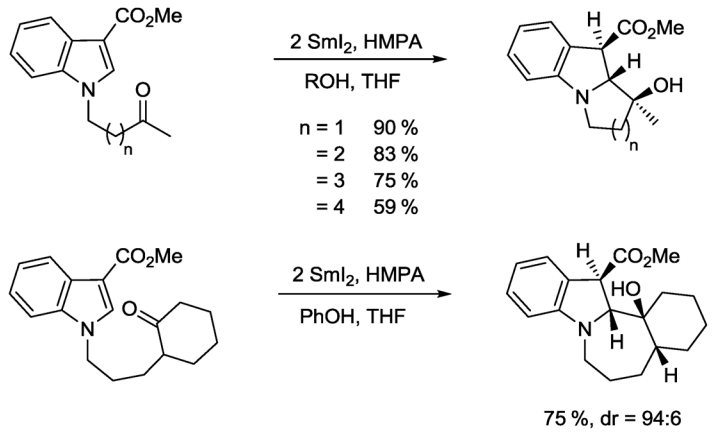
Synthesis of heterocycles

The introduction of nitrogen into the spacer unit between the carbonyl group and the arene ring or into the arene itself should allow the preparation of new functionalized heterocycles. Therefore, we studied first the use of suitably substituted β-amino ketone derivatives as well as aniline derivatives in the samarium ketyl-arene coupling. The expected products were received in moderate to good yields and generally with excellent diastereoselectivity [15]. Incorporation of the nitrogen atom into the aryl moiety is the second option. Whereas we did not obtain satisfying results with pyridine derivatives, the use of quinolines as ketyl accepting group was fairly successful. The developed method makes azasteroid derivatives accessible in a stereoselective fashion [16].

The most interesting heterocyclic system we studied so far involves indoles. Simple examples of N-alkylated indoles are depicted in Scheme 9 demonstrating that the formation of 5- or 6-membered rings proceeds with reasonable efficacy [17]. After these first successful cyclization reactions, we switched to more electron-deficient indole derivatives shown in Scheme 10 [18]. They very efficiently provided tricyclic and tetracyclic products with a remarkably functionalized dihydroindole substructure.



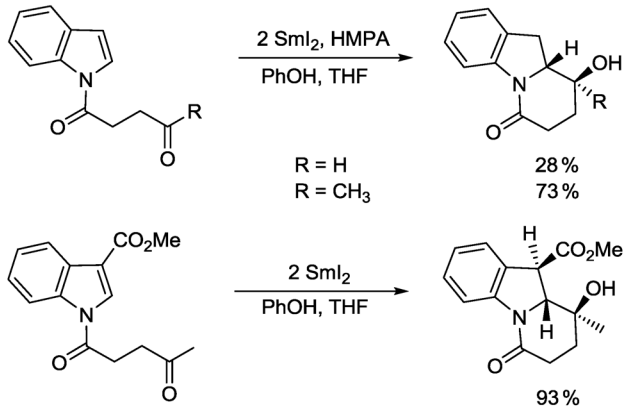
Scheme 9 SmI_2-induced cyclizations of N-alkylated indole derivatives.



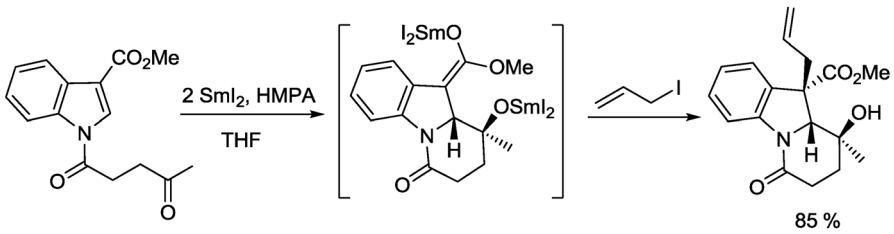
Scheme 10 SmI_2-induced 5-*exo-trig* to 8-*exo-trig* cyclizations of N-alkylated indole derivatives.

Furthermore, the stereoselectivities are often very high and the relative configuration of up to four stereocenters is controlled. It should be mentioned here that similar experiments were earlier reported by Fang et al., however, this group did not isolate the expected dihydroindole derivatives but the corresponding rearomatized indoles [19]. Also, an alternative electrochemical cyclization process has been published by Kise giving similar products with good diastereoselectivities [20].

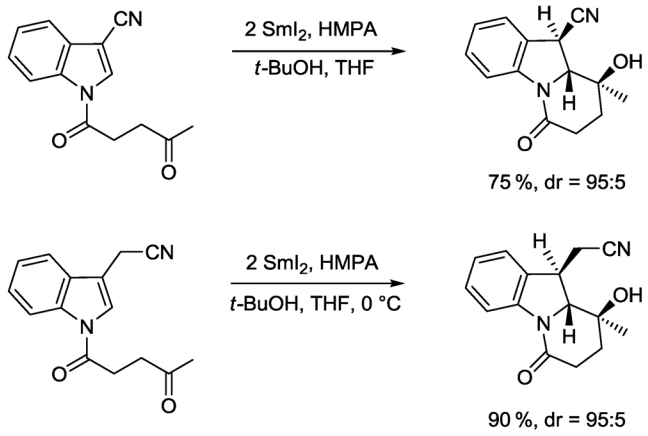
Employing N-acylated indole derivatives further increased the facility of the ketyl-indole coupling (Scheme 11) [17,18]. When the accepting indole moiety bears an electron-withdrawing substituent at C-3, it is possible to avoid the use of a proton source during cyclization. The corresponding samarium enolates can be smoothly trapped by electrophiles such as allyl iodide (Scheme 12). We could extend our methodology also to 3-cyano and 3-cyanomethyl substituted indole derivatives (Scheme 13) showing the generality of this samarium ketyl-indole coupling process [21]. The transformations presented in Schemes 9–13 and similar reactions opened a new route to highly functionalized indole derivatives. Owing to the privileged nature of the indole substructure among natural products and biologically active substances (including drugs in the market) it is clear that the reactions described here have a high potential for further applications.



Scheme 11 Results for SmI_2-induced cyclizations of N-acylated indole precursors.



Scheme 12 Cyclization of an N-acylated indole precursor and subsequent trapping with allyl iodide.

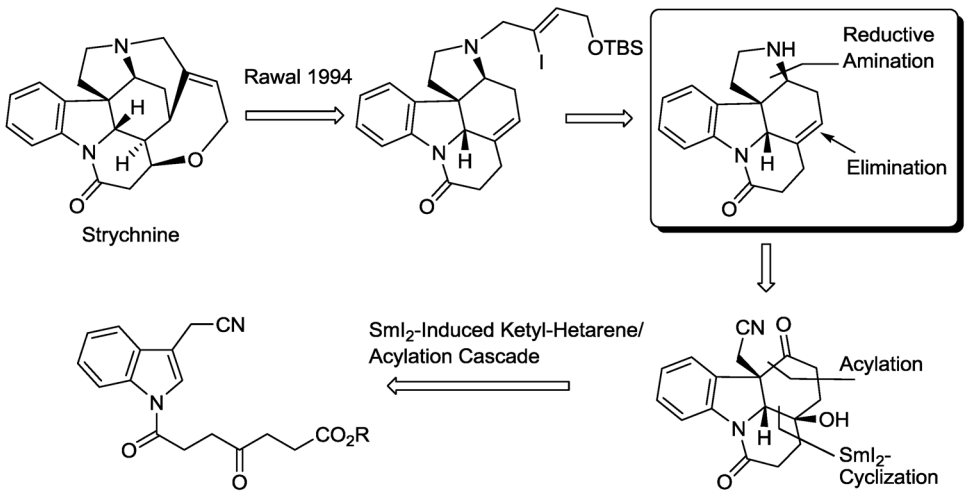


Scheme 13 SmI_2-induced cyclizations of cyano and cyanomethyl substituted indole derivatives.

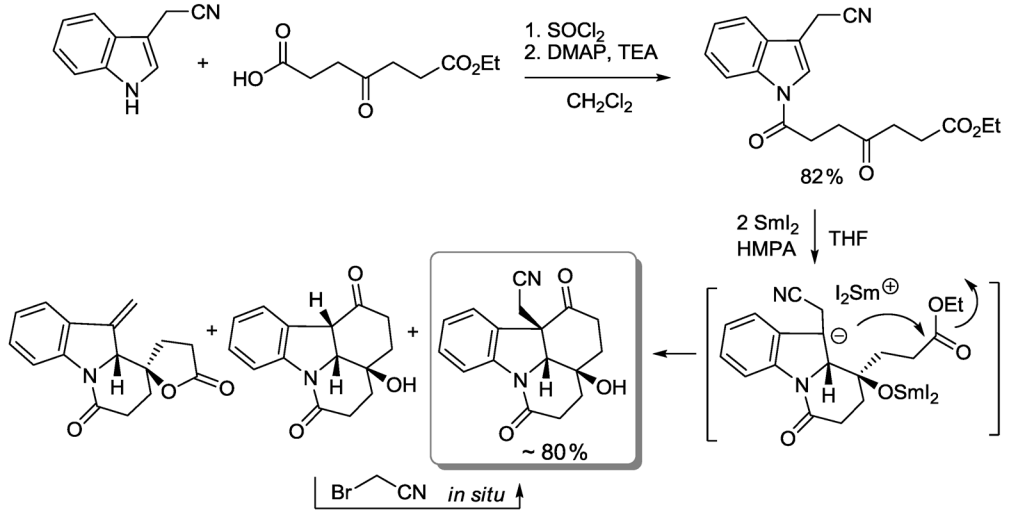
A short formal total synthesis of strychnine

As an impressive example of the potential of the ketyl-hetarene coupling we developed the so far shortest route to the alkaloid strychnine—one of the most famous and still challenging targets in organic synthesis [22]. Our retrosynthetic analysis aims for Rawal's pentacyclic intermediate as depicted in Scheme 14 [23]. This compound should be accessible from a tetracyclic cyclization product tracing back to the very simple acylated indol-3-yl acetonitrile derivative as precursor. This starting material is easily accessible from commercially available compounds and already contains all atoms required for the synthesis of the crucial Rawal pentacycle.

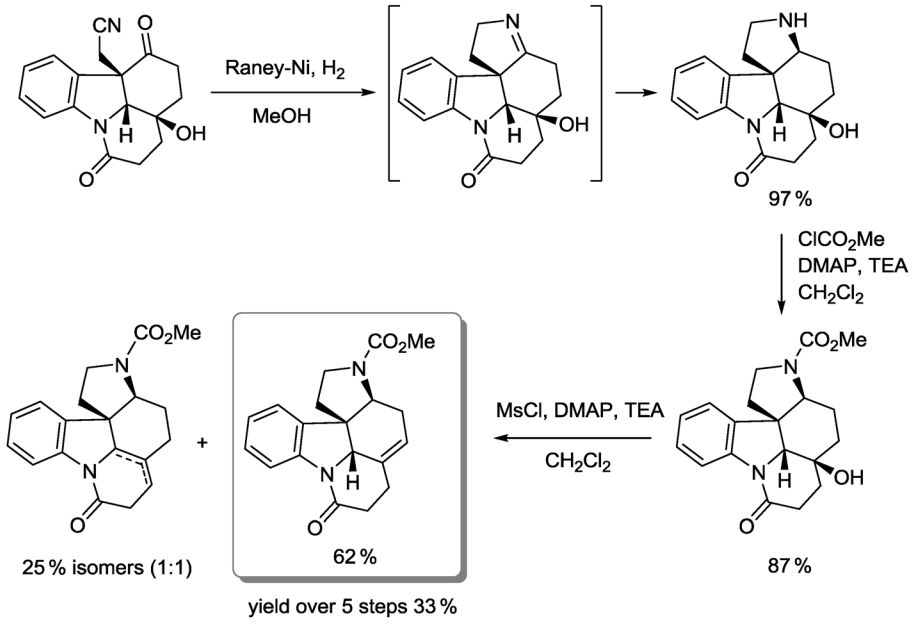
Most pleasingly, the anticipated SmI_2-induced ketyl-indole coupling/acylation cascade reaction proceeded very smoothly, affording the desired tetracyclic product in very good yield and as a single diastereomer (Scheme 15) [24]. The side product (ca. 5 %) formed by a reductive elimination could be converted back to the tetracyclic product by addition of bromoacetonitrile to the reaction mixture. By this procedure, the tetracyclic product was obtained in gram quantities in up to 80 % yield. After some experimentation, we found that exhaustive Raney-nickel reduction is the most efficient way to generate the fifth required ring in a stereoselective fashion (Scheme 16). Hence, just two steps generate the crucial pentacyclic system in very high atom efficacy and without use of any protective group. After conversion of the secondary amine to a carbamate—this is the only protective group employed in our approach to Rawal's compound—a modestly regioselective elimination generated the key target product with the double bond in the correct position.



Scheme 14 Retrosynthetic analysis of strychnine based on Rawal's key building block and a SmI_2-induced cascade reaction.

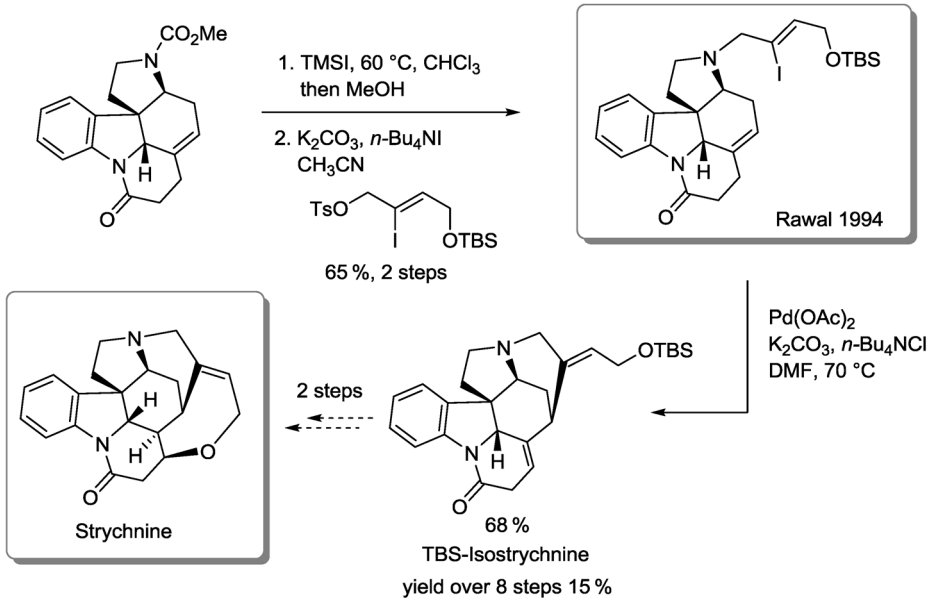


Scheme 15 Synthesis of starting material and the SmI_2-induced cascade reaction leading to the tetracyclic intermediate.



Scheme 16 Synthesis of protected strychnine precursor.

Deprotection of the key carbamate furnished the fairly unstable Rawal pentacycle which was further converted into an N-alkylated product also prepared by this research group. To unambiguously prove the relative configuration of the obtained products, we also executed the Heck reaction forming the sixth ring and furnishing *tert*-butyldimethylsilyl (TBS)-protected isostrychnine as reported by Rawal et al. (Scheme 17) [23]. They also described the two final steps to the racemic natural product.

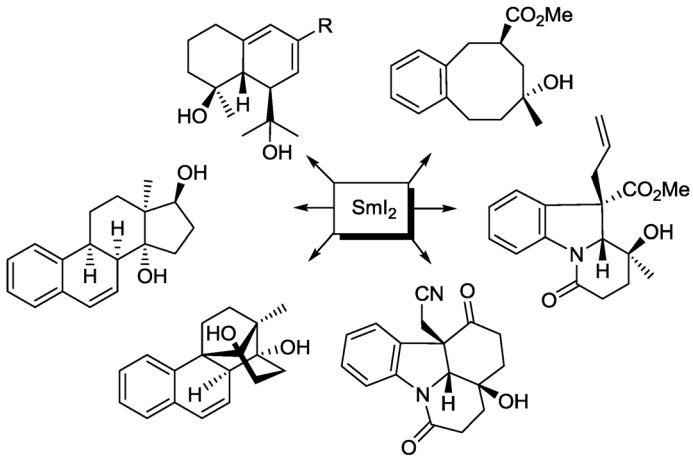


Scheme 17 Formal total synthesis of strychnine.

We could obtain the TBS-protected isostrychnine in 8 steps (with respect to commercially available compounds) and with an overall yield of 15 %, which constitutes the shortest and most efficient route to strychnine so far known [24]. This success demonstrates the applicability of samarium ketyl-(het)arene cyclizations in the synthesis of remarkably complex target molecules.

CONCLUSION

In summary, our journey from fairly simple samarium ketyl-alkene and -alkyne couplings to ketyl-arene and -hetarene couplings nicely demonstrate the versatility and usefulness of SmI_2-induced cyclization processes. Typical products are depicted in Scheme 18. Of special interest is the serendipitously discovered novel ketyl-arene coupling leading to hexahydronaphthalene derivatives starting from simple arenes. Extension to naphthalenes as ketyl accepting units furnishes steroid-like compounds. The synthesis of highly functionalized heterocyclic compounds is possible by different approaches, the samarium ketyl-indole coupling being of most interest as highlighted by the shortest formal total synthesis of strychnine. Many other applications aiming to complex carbocyclic or heterocyclic products can be envisioned by the use of the described dearomatizing ketyl-(het)arene coupling process.



Scheme 18 SmI_2-induced cyclizations of (het)arene ketones leading to cyclooctene, hexahydronaphthalene, hexahydroquinoline, or dihydroindole derivatives.

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